Failure mode and effects analysis to reduce risk of anticoagulation levels above the target range during concurrent antimicrobial therapy

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Warfarin is an anticoagulant prescribed to more than 30 million patients annually in the United States. It is used to treat patients with prothrombotic diseases, but its narrow therapeutic range requires the monitoring of the patient’s International Normalized Ratio (INR). Patients whose INR value are greater than 4.5 have an increased risk of major bleeding events, whereas those with an INR of <2 have an increased risk of adverse clotting events. Without proper dose adjustments and monitoring, patients are at increased risks of hospitalization, longer lengths of stay, and a higher 30-day mortality rate. Despite outpatient warfarin monitoring programs, warfarin continues to be a principal medication associated with adverse events, resulting in more than 30,000 emergency department visits annually in the United States.

Although all antimicrobials can potentially increase the INR, Clark et al. found that selected highly potentiating antimicrobials (HPAs) notably increased the INR in patients who received antimicrobial and warfarin therapy compared with control patients who only received warfarin.

**Purpose.** A failure mode and effects analysis (FMEA) was conducted to analyze the clinical and operational processes leading to above-target International Normalized Ratios (INRs) in warfarin-treated patients receiving concurrent antimicrobial therapy.

**Methods.** The INRs of patients on long-term warfarin therapy who received a course of trimethoprim–sulfamethoxazole, metronidazole, fluconazole, miconazole, or voriconazole (highly potentiating antimicrobials, or HPAs) between September 1 and December 31, 2011, were compared with patients on long-term warfarin therapy who did not receive any antimicrobial during the same period. A multidisciplinary team of physicians, pharmacists, and a systems analyst was then formed to complete a step-by-step outline of the processes involved in warfarin management and concomitant HPA therapy, followed by an FMEA.

**Results.** Patients taking trimethoprim–sulfamethoxazole, metronidazole, or fluconazole demonstrated a significantly increased risk of having an INR of >4.5. The FMEA identified 134 failure modes. The most common failure modes were as follows: (1) electronic medical records did not identify all patients receiving warfarin, (2) HPA prescribers were unaware of recommended warfarin therapy when HPAs were prescribed, (3) HPA prescribers were unaware that a patient was taking warfarin and that the drug interaction is significant, and (4) warfarin managers were unaware that an HPA had been prescribed for a patient.

**Conclusion.** An FMEA determined that the risk of adverse events caused by concomitantly administering warfarin and HPAs can be decreased by preemptively identifying patients receiving warfarin, having a care process in place, alerting providers about the patient’s risk status, and notifying providers at the anticoagulation clinic.
Warfarin is metabolized through the cytochrome P-450 (CYP) isoenzyme system, specifically CYP2C9, which is inhibited by HPAs. Trimethoprim–sulfamethoxazole, metronidazole, fluconazole, voriconazole, and miconazole are considered HPAs because they inhibit CYP metabolism.12–14 The interaction between warfarin and HPAs results in appreciably increased INRs and is frequently missed by outpatient warfarin monitoring programs.11,15–18 For example, the addition of trimethoprim–sulfamethoxazole to warfarin therapy resulted in INR increases of ≥2 in more than one third of patients.13,14,19 Although a preemptive dose adjustment of warfarin by 10–20% at the initiation of an HPA regimen can prevent INR fluctuations, this adjustment is not routinely performed in clinical practice.14 The known interaction and possible intervention have not been well studied in adverse-drug-event reporting and quality-improvement projects.20 The purposes of this study were to identify the comparative frequency of INR levels above the target range in patients on long-term warfarin who received an HPA and to analyze the clinical and operational processes leading to INR levels above the target range.

Methods

Retrospective cohort study. This study was conducted at a tertiary medical center with a closed healthcare delivery system, an electronic medical record (EMR), and electronic prescription capability. This study was reviewed by the institutional review board at our institution and determined to be a nonresearch, quality-improvement project; informed consent for record review was not required. Baseline data were collected through retrospective cohort analysis evaluating follow-up INRs and adverse events among outpatients. The INRs of patients on long-term warfarin therapy who received a course of trimethoprim–sulfamethoxazole, metronidazole, fluconazole, miconazole, or voriconazole between September 1 and December 31, 2011, were compared with patients on warfarin therapy who did not receive any antimicrobial during the same period. Patients were excluded if they were younger than 18 years, were hospitalized, had an invasive procedure during the period of analysis, were receiving a long-term stable regimen of an antimicrobial, or did not have an INR measured within two weeks of antimicrobial initiation for case patients or during a randomly selected two-week period from October 24 through November 7, 2011, for control patients. Patients were identified through the EMR, which had a built-in pharmacy notification regarding an interaction with warfarin. This notification stated there was a severe interaction and was passively displayed on the side panel of the electronic prescription screen. This notification did not require any acknowledgment by the prescriber nor did it provide a recommendation of action to the provider.

Of the patients for whom an HPA was prescribed, the performance of an INR check or warfarin dose adjustment was noted in the EMR when performed. Manual review of the EMR was performed to obtain the goal INR, the measured INR, and adverse events of each case patient for two weeks following initiation of the antimicrobial and of each control patient for the selected two weeks. Fisher’s exact test was used to compare proportions of case patients with control patients who had INR levels below the target range, INR levels within the target range, INR levels greater than 4.5, INR levels greater than 6, and adverse events. A correction factor of 0.05 per cell was used to estimate risk ratios for which the result would have otherwise been undefined.

Patients were included regardless of where their warfarin therapy was managed (e.g., anticoagulation clinic, primary care physician). The anticoagulation providers were a combination of nurses, pharmacists, and physicians. Even if the patients were enrolled in an anticoagulation clinic, there was no protocol for notifying the anticoagulation clinic about the HPA prescription or standard protocol of how to manage the patient’s warfarin with the new HPA prescription.

Failure mode and effects analysis. A multidisciplinary team of physicians, pharmacists, and a systems analyst was formed to complete a step-by-step outline of the processes involved in warfarin management and concomitant HPA therapy (i.e., a “process walk”), followed by failure mode and effects analysis (FMEA).21 Based on steps identified in the process walk, a list of potential failure modes was created. Each failure mode was assigned a numeric value to represent the rate of occurrence, severity, and likelihood of detection; all team members had to agree on this value. A severity score of 1 was assigned when there was no potential danger (i.e., no patient or system injury), and a score of 10 indicated there was the potential for severe danger (i.e., patient death or system failure). An occurrence score of 1 meant that there was a remote chance of occurrence (i.e., not known to have occurred); a score of 10 indicated that failure was certain (i.e., occurring every time). A likelihood of detection score of 1 was assigned when detection of a possible error was almost certain (i.e., a hard stop in place); a score of 10 was assigned when no chance of error detection existed (i.e., no set mechanism in place).

Each failure mode was then given a risk priority number (RPN) determined through multiplying the occurrence, severity, and likelihood numbers previously assigned. The top 30 failure modes were considered high risk with a corresponding RPN.
of >250. The highest-priority failure modes were discussed separately and given a proposed intervention. In total, 20 interventions were proposed to help reduce the highest-priority failures. A highest-risk failure mode’s total RPN was calculated by adding all RPNs corresponding to the individual high-risk failure modes. Then, each proposed intervention was prioritized by adding the associated RPN values for each failure mode affected by the intervention. The interventions were ranked in accordance with their RPN, with the first proposed intervention having the highest RPN. The additional benefit, or the benefit of adding another intervention, was determined by calculating the remaining high-risk failure modes’ RPNs that were addressed through an additional intervention. It was represented as a percentage of the highest-risk failure mode’s total RPN.

To visualize the potential impact of a given intervention, as well as a combination of interventions, we created a Pareto diagram. The Pareto diagram charted each intervention with its individual RPN, as well as the cumulative percentage of the total RPN value affected by the additional interventions.

Finally, a subjective effort:benefit analysis was used to determine which set of interventions would most benefit the overall problem. Effort was determined subjectively, weighing such factors as cost, difficulty of mechanics of implementation, and negative unintended downstream effects. Benefit was determined subjectively by estimating the overall magnitude of the intervention. An effort:benefit chart was then constructed with these two subjective variables.

Results

A total of 207 patients receiving an HPA who had an INR recorded within two weeks of prescription were identified. Among these patients, we identified 69 case patients prescribed

<table>
<thead>
<tr>
<th>Variable by Concurrent Antimicrobial Used</th>
<th>Therapeutic INR</th>
<th>Supratherapeutic INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim–sulfamethoxazole (n = 69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) pts</td>
<td>21 (30)</td>
<td>112 (0.77–1.02)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.39 (1.01–1.91)</td>
<td>0.55</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>0.23</td>
</tr>
<tr>
<td>Metronidazole (n = 21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) pts</td>
<td>7 (33)</td>
<td>1.33 (0.60–2.26)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>0.78 (0.48–1.28)</td>
<td>0.33</td>
</tr>
<tr>
<td>p-value</td>
<td>0.03</td>
<td>0.23</td>
</tr>
<tr>
<td>Fluconazole (n = 21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) pts</td>
<td>5 (24)</td>
<td>1.40 (0.61–2.44)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>0.83 (0.43–1.59)</td>
<td>0.33</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>Control group (n = 957)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) pts</td>
<td>26 (27)</td>
<td>0.14 (0.00–0.83)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>Reference value</td>
<td>Reference value</td>
</tr>
<tr>
<td>p-value</td>
<td>Reference value</td>
<td>Reference value</td>
</tr>
</tbody>
</table>

Note: Values are given as the number of patients (percentage) with an INR greater than 4.5 or 6.0. Relative risks and 95% confidence intervals (CI) were calculated using Fisher’s exact test. The relative risk of 1.0 indicates no difference in the risk of the event compared to the control group. Adverse events included hematuria and delayed biopsy due to increased INR in the group that received trimethoprim–sulfamethoxazole, and hematochezia and gingivorrhagia in the group that received fluconazole.
Figure 1. Process map of warfarin monitoring and outpatient highly potentiating antimicrobial (HPA) ordering used at Mayo Clinic Rochester. INR = International Normalized Ratio, NP/PA = nurse practitioner or physician assistant.
Pt believed to be at risk or has an infection

START

Provider assesses the risk of infection

Treatment of infection or prophylaxis?

START

Provider assesses the risk of infection

Treatment of infection or prophylaxis?

START

Provider assesses the risk of infection

Treatment of infection or prophylaxis?

START

Provider assesses the risk of infection

Treatment of infection or prophylaxis?

START

Provider assesses the risk of infection

Treatment of infection or prophylaxis?

START

Provider assesses the risk of infection

Treatment of infection or prophylaxis?

START

Provider assesses the risk of infection

Treatment of infection or prophylaxis?

START

Provider assesses the risk of infection

Treatment of infection or prophylaxis?

START

Provider assesses the risk of infection

Treatment of infection or prophylaxis?

START

Provider assesses the risk of infection

Treatment of infection or prophylaxis?

START

Provider assesses the risk of infection

Decision-making criteria:
1. Efficacy (past exposure, spectrum)
2. Organ function
3. Safety in terms of allergies
4. Cost and convenience for pt
5. Drug interaction

Decide the best antimicrobial to prescribe

Prescribing HPA?

START

Enter prescription into the computer

Acknowledge warnings, and confirm prescription

Electronically prescribing?

Yes

No

Prescription goes directly to pharmacy

Provider signs the printout/provider calls pharmacy

Pharmacy receives an order/request

Verify whether it is the right prescription

Is change of prescription necessary?

Yes

No

Notify provider

Dispense HPA

No

END (out of scope)
trimethoprim–sulfamethoxazole, 21 case patients prescribed metronidozole, and 21 case patients prescribed fluconazole who met inclusion criteria. In addition, 957 control patients who received warfarin and no antimicrobial were identified. No case patients were identified who had been prescribed miconazole or voriconazole. The anticoagulation clinic was not notified when an HPA was prescribed to patients treated with warfarin, and no patient had a warfarin dose adjustment at the time of HPA prescription. Table 1 summarizes the INR measurements and clinical outcomes of patients in both groups.

Patients taking trimethoprim–sulfamethoxazole, metronidazole, or fluconazole demonstrated a significantly increased risk of having an INR of >4.5 (Table 1). Three adverse events occurred: hematuria (INR, 6.6) with trimethoprim–sulfamethoxazole, hematochezia (INR, 6.3) with fluconazole, and gingi-

<table>
<thead>
<tr>
<th>Identified High-Risk FM*</th>
<th>Intervention*</th>
<th>FM Count</th>
<th>RPN Count</th>
<th>Additional Benefit, %c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Identify all patients taking long-term warfarin therapy in electronic medical record</td>
<td>18</td>
<td>7860</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>Signing of the HPA prescription initiates process to standardize care in warfarin dose adjustment and INR follow-up</td>
<td>11</td>
<td>4260</td>
<td>7.4</td>
</tr>
<tr>
<td>3</td>
<td>Alert providers at point of prescription of an HPA for a patient taking warfarin</td>
<td>10</td>
<td>3960</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Alert warfarin managers about prescription of an HPA</td>
<td>4</td>
<td>2570</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Alert pharmacy about prescription of an HPA</td>
<td>4</td>
<td>2300</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Improve medication reconciliation processes</td>
<td>4</td>
<td>1710</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Warfarin manager contacts patients within 24 hr of the prescription of an HPA</td>
<td>3</td>
<td>1670</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Inform warfarin manager about dosage change of warfarin</td>
<td>3</td>
<td>1670</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Develop a rating (color coding) system for alerts to avoid low-frequency alerts</td>
<td>2</td>
<td>1530</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Insert reason for disregarding alerts when prescribing an HPA</td>
<td>2</td>
<td>1530</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>Assess reason why HPA alert is overridden and provide education accordingly</td>
<td>2</td>
<td>1530</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>Knowledge management shares warfarin management care process model with local pharmacies</td>
<td>2</td>
<td>1380</td>
<td>2.8</td>
</tr>
<tr>
<td>13</td>
<td>Educate providers on the interaction between warfarin and HPAs</td>
<td>2</td>
<td>720</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>Require warfarin managers to insert reason for disregarding alerts</td>
<td>2</td>
<td>700</td>
<td>6.5</td>
</tr>
<tr>
<td>15</td>
<td>Publish warfarin protocol to local pharmacies</td>
<td>2</td>
<td>630</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>Pharmacy alerts prescriber of HPA after prescription not picked up by the patient in set amount of time</td>
<td>2</td>
<td>600</td>
<td>5.6</td>
</tr>
<tr>
<td>17</td>
<td>Provide online patient education material</td>
<td>1</td>
<td>480</td>
<td>4.5</td>
</tr>
<tr>
<td>18</td>
<td>Develop standard algorithm to assist with clinical decision-making</td>
<td>1</td>
<td>480</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>Enhance patient education through education fliers</td>
<td>1</td>
<td>480</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>Reorganize patient education material in culturally appropriate context</td>
<td>1</td>
<td>400</td>
<td>0</td>
</tr>
</tbody>
</table>

*For prioritization, each failure mode (FM) was given a corresponding risk priority number (RPN) by multiplying relative occurrence, severity, and likelihood of the FM. This calculation resulted in 30 identified high-risk FMs with a RPN of >250. HPA = highly potentiating antimicrobial, NA = not applicable, INR = International Normalized Ratio.

Interventions were proposed to correct the 30 high-risk FMs. Each intervention was given an RPN count that totaled the FM RPNs addressed with the intervention.

*Determined by calculating the other high-risk FM RPNs addressed with each additional intervention. This additional benefit was shown as a percentage of the highest-risk FM’s total RPN.
vorrhagia (INR, 9.0) with fluconazole. Among the patients who received trimethoprim–sulfamethoxazole, metronidazole, or fluconazole, only 25% of their care providers remarked in the EMR on the interaction of the antimicrobial with warfarin.

The results of the process walk for warfarin monitoring and HPA prescription are summarized in Figure 1. The FMEA identified 134 failure modes. Of these modes, 124 were determined to have a severity score of 10, 28 were determined to occur at least monthly (occurrence score of >5), and 115 did not have an automated system of detection in place (likelihood of detection score of >3). Thirty high-risk failure modes (RPN of >250) were identified. The four highest-risk failure modes were as follows: (1) EMRs did not identify all patients receiving warfarin, (2) HPA prescribers were unaware of recommended warfarin therapy when HPAs were prescribed, (3) HPA prescribers were unaware that a patient was taking warfarin and that the drug interaction is noteworthy, and (4) warfarin managers were unaware that an HPA had been prescribed for a patient.

A total of 20 interventions were analyzed using a Pareto diagram to address the failure modes (Table 2 and Figure 2). A collective group of 4 interventions were found quantitatively most effective: (1) ensure that the EMR identified all patients taking warfarin, (2) ensure electronic access of a standardized care process model for INR monitoring and warfarin dose adjustment for patients taking HPAs, (3) create an alert in the EMR for providers at the point of prescribing an HPA for a patient already receiving warfarin, and (4) create an automated alert to the patient’s anticoagulation clinic whenever an HPA is prescribed. Effort:benefit analysis found that the greatest risk reduction for the effort needed for intervention was likely to be attained by enacting all 4 interventions. Given these interventions and the effort:benefit analysis, we estimated that more than half of the potential adverse events related to this medication interaction would be avoided.

**Discussion**

Warfarin has a notable interaction with several antimicrobials that are often prescribed without accounting for these known interactions. This study used a retrospec-

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**Figure 2.** Pareto diagram used to prioritize recommendations. Each proposed intervention is depicted as a bar, with the highest-impact intervention on the left. The additional benefit of adding another intervention to previous interventions is depicted as the percentage of the cumulative impact.
tive cohort analysis to define the magnitude of this problem at one institution. Patients taking warfarin long-term for whom trimethoprim–sulfamethoxazole, metronidazole, or fluconazole was prescribed had a significantly increased risk of an INR of >4.5 ($p < 0.001, p = 0.03$, or $p < 0.0011$, respectively). This increase in the INR may result in additional dose adjustments, office visits, and adverse events. Our study found that only half of the patients for whom an HPA was prescribed had an INR level taken within two weeks. Because HPAs can cause dangerously high INRs (>4.5) within two to six days of initiation, it is possible that many of these unmonitored patients had a clinically notable bleeding risk that was unknown to their providers.\(^3,12,24\)

FMEA identified over 130 specific failure modes potentially contributing to these adverse events (INR of >4.5 and bleeding events). This study was unique because it not only showed the possible consequences of administering warfarin with HPAs but also semiquantitatively established how to best intervene on the basis of a systematic analysis. Multiple studies have evaluated specific failure modes that lead to adverse events and have proposed limited interventions to reduce these adverse events. Previous solutions have included outpatient monitoring programs, set-interval monitoring of INRs, and preemptive warfarin dose adjustment.\(^1,13,14\) Despite these single interventions on specific failure modes, a number of adverse events have occurred.\(^1,14\)

Our study used a systematic approach to identify multiple failure modes with multiple potential interventions. In reality, each patient has a unique interaction with the healthcare system that results in multiple potential failure modes. In addressing a single failure mode, other failure modes specific to a unique population may be missed. For example, alerting the outpatient warfarin monitoring program when an HPA is prescribed limits the scope to patients already monitored by the outpatient program. However, a systematic approach would recognize the population not in the anticoagulation clinic, who would have been missed by this intervention otherwise.

Another disadvantage of evaluating single failure modes is that they are often not independent of the other potential failure modes. This characteristic is highlighted by the example of notifying a provider to check an INR when prescribing an HPA to a patient receiving warfarin. This intervention on a single failure mode assumes that the patient is appropriately identified as taking warfarin in the system. In a systematic approach, both failure modes—identifying patients taking warfarin and providers not checking INRs—would be recognized and addressed. Our systematic approach addressed these distinct patient populations and the dynamic interactions that result in multiple failure modes in a given system. In doing so, we were able to demonstrate that more than one intervention is required to best avoid patient adverse events due to multiple failure modes. Further studies are needed to assess the impact of multiple interventions on the percentage of INR levels above the target range in patients taking warfarin for whom an HPA is prescribed.

Our study had some limitations. Due to the small sample size and low power, we were unable to reliably estimate the relative risk for bleeding events. We also included patients with an INR measured within two weeks of starting an HPA, possibly introducing selection bias toward patients believed to be at higher risk for an elevated INR by their provider. However, our finding of increased INRs in patients receiving an HPA corroborates similar findings by Clark et al.,\(^11\) who used ill control patients.\(^25\)

As a limitation of the generalizability of the study, our proposed solution assumes that a healthcare system has an outpatient warfarin monitoring program and a unified EMR. Unfortunately, this assumption limits these proposed interventions to similarly integrated health systems. We also assumed that patients were part of a closed health system and were not receiving their care from multiple health systems. Therefore, healthcare systems using independent medical records may not be able to incorporate our solutions. Although our specific group of interventions may not be globally applicable to all healthcare systems, our systematic approach may help to identify another health system’s failure modes and potential interventions.

**Conclusion**

An FMEA determined that the risk of adverse events caused by concomitantly administering warfarin and HPAs can be decreased by preemptively identifying patients receiving warfarin, having a care process in place, alerting providers about the patient’s risk status, and notifying providers at the anticoagulation clinic.

**References**


